IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| In re Application of: **EMBIL ET AL.** | ) | |
| Serial No.. **09/762,630** | ) | Art Unit: **1614** |
| Filed: **February 12, 2001** | ) | |
| For: **NIMESULIDE CONTAINING TOPICAL PHARMACEUTICAL COMPOSITIONS** | ) | Examiner: **Dwayne Jones** |

## DECLARATION UNDER 37 C.F.R. 1.132

I, Dr. Koral Embil, declare as follows:

1. My scientific education and experience is set forth in my attached resume.

2. I am one of the inventors of the invention claimed in the above-referenced application. I am familiar with the Office Action issued September 24, 2003, specifically with the rejection under 35 U.S.C. §103(a).

3. Under my direction the following experiments were performed. These experiments establish that more nimesulide is released using the compositions of the present invention than in the compositions described in the examples of Jain *et al.*, EP 0812587A1.

*Experiment*

In the following experiment, seven compositions were prepared. Two of the compositions were prepared as described in Examples 2 and 4 of Jain *et al.*, EP0812587A1. The remaining five examples were prepared as described in the above-referenced application.

| Example 4 (EP0812587A1) | % |
|---|---|
| Nimesulide | 1.00 |
| DimethylSulfoxide: | 10.50 |
| Glyceryl Monostearate | 8.00 |
| Mineral Oil | 31.00 |
| White Petrolatum | 48.50 |
| Water | 2.00 |

| Example 2 (EP0812587A1) | % |
|---|---|
| Nimesulide | 1.00 |
| Transcutol | 35.00 |
| Water | 10.00 |
| Disodium hydrogen phosphate | 0.10 |
| Cremorphor RH 40 | 5.00 |
| Labrifil M 1944 CS | 10.00 |
| Glyceryl monostearate | 8.00 |
| Stearic Acid | 13.00 |
| Ethyl Oleate | 2.90 |
| Diethyl Sulphoxide | 15.00 |

In the remaining compositions, prepared in accordance with the above-referenced application, the nimesulide was dissolved in DGME to form a clear solution, which was heated to 43-47°C. Glyceryl monoolein was heated to 43-47°C and mixed into the solution which was then cooled to room temperature. The mixing speed was increased and the hydroxypropylcellulose was added. Mixing continued until a clear gel was obtained.

| RFA 403 –50 | % |
|---|---|
| Transcutol | 78.00 |
| Nimesulide | 1.00 |
| Glyceryl MonoOleate | 20.00 |
| HydroxypropylCellulose | 1.00 |

| RFA 403 –55 | % |
|---|---|
| Transcutol | 75.00 |
| Nimesulide | 1.00 |
| Glyceryl MonoOleate | 23.00 |
| HydroxypropylCellulose | 1.00 |

| RFA 403 –56 | % |
|---|---|
| Transcutol | 72.00 |
| Nimesulide | 1.00 |
| Glyceryl MonoOleate | 26.00 |
| HydroxypropylCellulose | 1.00 |

| RFA 403 –57 | % |
|---|---|
| Transcutol | 69.00 |
| Nimesulide | 1.00 |
| Glyceryl MonoOleate | 29.00 |
| HydroxypropylCellulose | 1.00 |

| RFA 403 –58 | % |
|---|---|
| Transcutol | 66.00 |
| Nimesulide | 1.00 |

| | |
|---|---|
| Glyceryl MonoOleate | 32.00 |
| HydroxypropylCellulose | 1.00 |

Results

The *in vitro* release of nimesulide from each composition was determined by applying the composition through a cellophane membrane using a Franz Diffusion cell for predictive *in vitro* release. The results are set forth in Table I, below. As can be seen from the *in vitro* release studies of nimesulide, compositions RFA 403-50, RFA 403-55, RFA 403-56, RFA 403-57 and RFA 403-58 all of which contain only nimesulide, glyceryl monooleate, hydroxypropylcellulose and transcutol (diethylene glycol monoethyl ether) had significantly greater release of nimesulide than the compositions of Jain *et al.*

Table I
***IN VITRO* RELEASE STUDIES OF NIMESULIDE FROM THE SAMPLES**

| t(1/2) min. | EXAMPLE 4 EP0812687AI RFA 403-63 | EXAMPLE 2 EP0812687A1 RFA 403-62 | 1.25% NaCMC | RFA 402- 01 | RFA403-50 | RFA403-55 | RFA403-56 | RFA403-57 | RFA403-58 |
|---|---|---|---|---|---|---|---|---|---|
| 5.477226 | 0.009453 | 0.008864 | 0.028002 | 0.010987717 | 0.021198 | 0.014912 | 0.031042 | 0.036828 | 0.017462 |
| 7.745967 | 0.014552 | 0.014482 | 0.047968 | 0.019945087 | 0.033878 | 0.030888 | 0.044396 | 0.053024 | 0.033614 |
| 10.95445 | 0.020378 | 0.025645 | 0.068876 | 0.035532514 | 0.053362 | 0.055295 | 0.08651 | 0.092452 | 0.069251 |
| 13.41641 | 0.035691 | 0.037248 | 0.086612 | 0.048794075 | 0.070342 | 0.073253 | 0.104738 | 0.11432 | 0.090785 |
| 15.49193 | 0.037819 | 0.041149 | 0.103825 | 0.062509393 | 0.084277 | 0.089303 | 0.127363 | 0.148369 | 0.113796 |
| 17.32051 | 0.040445 | 0.04725 | 0.118043 | 0.07628685 | 0.097729 | 0.104742 | 0.145996 | 0.15115 | 0.132553 |
| 18.97367 | 0.053431 | 0.060109 | 0.136561 | 0.098683526 | 0.116809 | 0.125765 | 0.178055 | 0.201949 | 0.164231 |

Conclusion

The compositions of the above-referenced application provide a significantly higher rate of absorption of nimesulide than the compositions of Jain *et al.* This is clinically significant, because it would decrease the amount of nimesulide that had to be administered, increase the effectiveness of the composition administered, decreasing costs and the need for other analgesics or stronger doses of analgesics to be administered.

December 22, 2003
Date

Koral Embil, Ph.D.
Signature

# CURRICULUM VITAE

**October 6, 2003**

## NAME

Koral Embil, Ph. D.

## PERSONAL DATA

Date of Birth: July 26, 1951
Place of Birth: Istanbul, Turkey
Citizenship: Turkey

## PRESENT POSITION

Managing Director (Science & Technology)
Embil Pharmaceutical Co. Ltd.
P. O. Box 226 34380 Şişli
Istanbul, Turkey

## EDUCATION

H. S. - Sisli Terakki Lycee, Istanbul, Turkey Grad.- 1969

B. S. - University of Newcastle Upon Tyne, England- 1974
Department of Chemistry

M. S. - University of Florida, Gainesville, Florida- 1978
Department of Pharmaceutics
Advisor: Dr. G. Torosian
Thesis: Dissolution Behavior of commercial Enteric Coated Aspirin Tablets.

Ph. D. - University of Florida, Gainesville, Florida- 1981
Department of Pharmaceutics minoring in
Industrial Engineering.
Advisor: Dr. G. Torosian
Dissertation: The adsorption of Tricyclic Antidepressants on Solid Interfaces.

## TEACHING EXPERIENCE

Teaching assistant physical pharmacy, industrial manufacturing and pharmacokinetics, University of Florida (1976- 1981).

## PROFESSIONAL TRAINING

1981- 6 week training course, Von Heyden Fabrik, Subsidiary of Squibb Regensburg, Germany.

1982- Postdoctoral Scientist, Smith Kline and French Labs. Philadelphia, PA, U. S. A. (Jan-Nov 1982)

1984- Dialog Information Services Medline and Patents Database search training course, Pan Am Building New York NY ( 12- 14 April 1984 ).

1985- Basic Course of Pharmacokinetics and Biopharmaceutics sponsored by the University of Florida and the Freie Universitat Berlin. Prof. Karl Heinz Fromming and Prof. E. R. Garrett, Bad Lauteberg, Germany. ( June 2, 1985 )

1990- Quality Assurance of Solid Dosage forms, Istanbul, Turkey, Hacettepe University and Bristol Myers Squibb Co. USA. ( 10- 12 December 1990 )

1990- Financial Problems and Annual Evaluation in Companies, Dünya gazetesi, Prof. Veysi Sevig. ( 17- 21 December 1990 )

1990- Financial Problems and Annual Evaluation in Companies, Dünya gazetesi, Prof. Veysi Sevig. ( 26- 30 December 1990 )

1993- Eudragit Workshop, Film Coating Techniques, Stuttgart, Germany. ( 4- 6 May 1993 )

1993- Owner President Management Program, Harvard University, Business School, Boston, USA. 3 week courses in 1991, 1992, and 1993. Graduation Date: August 1993 ( OPM 20 ).

1996- International Licensing of Strategic Partnering for today's Technical Manager. The Center for Professional Advancement, Amsterdam, Netherlands. ( 28- 31 October 1996 )

1997- Microencapsulation of Particle Coating. The Center for Professional Advancement, Amsterdam, Netherlands. ( 5- 8 October, 1997 )

1997- High Performance Presentation Skills, Rostrum Personal Development, London , England. ( 29- 30 April, 1997 )

1998- Fundamentals of Molecular Biology and Genetic Engineering, The Center for Professional Advancement, Amsterdam, Netherlands. ( 20- 23 April, 1998 )

1999- Regulation And Application Seminar, Istanbul. ARC Eğitim, Hakan Çınar.
( 30 January 1999)

## PROFESSIONAL AFFILIATIONS

1990- present Turkish pharmacists Association.
1991- present American Pharmaceutical Association ( AphA ), Associate Member.
1994- present Controlled Release Society, Inc.
1996- present American Academy of Dermatology ( AAD ), Affiliate Member.

## PAPERS PUBLISHED

**Masters Thesis:**

Dissolution behavior of commercial enteric coated aspirin tablets, University of Florida, 1978, Gainesville, Florida, USA.

Publisher: University Microfilms International, 300 N. Zeeb Rd. Ann Arbor, MI 48106.

**Dissertation:**

The adsorption of tricyclic antidepressants on solid interfaces, University of Florida, 1981, Gainesville, Florida, USA.

Publisher: University Microfilms International, 300 N. Zeeb Rd. Ann Arbor, MI 48106.

## PUBLICATIONS

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2. Embil, K., Torosian, G., Effect of instrumental vibration levels on dissolution. J. Pharm. Sci. 68, 1336 ( 1979 ).

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4. Embil, K., Torosian G. Solubility and ionization characteristics of doxepin and desmethyldoxepin. J. Pharm. Sci. 71, 191 ( 1982 ).

5. Embil, K., Polli, G.P., Chong, C.W., Caldwell, H.C., and Ravin L.J. An automated dissolution procedure for controlled release dosage forms. Pharmaceutical Technology. 7, 62 ( 1983 ).

6. Sun, J.X.S., Embil, K., Chow, D.S.L., Lee, C.C.S. High Performance liquid chromatographic analysis, plasma protein binding and red blood cell partitioning of phenprobamate. Biopharm. Drug Dispos. 8, 341 ( 1987 ).

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9. Embil, K., and Nacht, S., Microsponge Delivery Systems (MDS). A topical delivery system with reduced irritancy incorporating multiple mechanisms for triggering release of the actives. Journal of Microencapsulation 13, 575 ( 1996 ).

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## ABSTRACTS

1. Embil, K. And Torosian, G. Dissolution behavior of commercial enteric coated aspirin tablets. 1978 abstracts, 23rd American Pharmaceutical Association / Academy of Pharmaceutical Sciences National Meeting, Hollywood, Fla., USA, November 1978.

2. Embil, K. and Torosian, G. Solubility and ionization characteristics of doxepin and desmethyldoxepin. 1981 abstracts, 128th American Pharmaceutical Association Annual Meeting, St. Louis, MO. USA, April 1981.

3. Embil, K. Automated dissolution procedures for sustained release dosage forms. 1984 abstracts, XVIII Semaine Balkanique, Istanbul Turquie., 30 Aout-4 September 1984.

4. Embil, K., Accelerated stability testing: isothermal versus nonisothermal methods, 1984 abstracts, 2nd International Symposium on Pharmaceutical Technology. Ankara, Turkey, October 3-5, 1984.

5. Chow, D.S., Sun, X.S., Wang, T.I., Embil, K. and Lee, C.S. HPLC analysis of phenprobamate and acetominophen in rat serum. 1984 abstracts, 37th National Meeting and exposition. American Pharmaceutical Association Academy of Pharmaceutical Sciences, Philadelphia Pa., USA November 1984.

6. Sun, J., Chow, D., Embil, K. and Lee, C.S. Phenprobamate kinetics in rats. 132nd American Pharmaceutical Association Annual Meeting and 38th National Meeting of the Academy of Pharmaceutical Sciences, San Antonio, Texas, USA February 16-21, 1985.

7. Townsend, R., Embil, K., Perrin, J.H. and Derendorf, H., Determination of Dissolution Profiles of Tablets Containing Conjugated Estrogens using HPLC analysis., 3rd International Pharmaceutical Technology Symposium, Ankara, Turkey, September 9-11, 1986.

8. Embil, K., Nacht, S., Microsponge Delivery Systems ( MDS ). A topical delivery system with reduced irritancy incorporating multiple mechanisms for triggering release of the actives. 1993 Minutes, 9th International Symposium on Microencapsulation, Ankara, Turkey, September 13-15, 1993.

9. Embil, K., The Microsponge topical Drug Delivery System and it's commercial applications. 1997 5th International Symposium of Pharmaceutical Sciences ( ISOPS-5 ) Ankara University, Faculty of Pharmacy, Ankara, Turkey, June 24-27, 1997.

10. C. E. Taner, E. S. Yücel, M. İnce, K. Embil ( sp ), Vaginitis and Treatment. 8th International Congress On Infectious Diseases, Boston, USA. 15- 18 May, 1998.

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12. Senorkyan, L., D, Kara., Embil. K., and Baktır. G., Comparision of the in vitro diffusion of Nimesulide from commercially available gel formulations. Perspectives in Percutaneous Penetration, 8th International Conference, Antibes/Juan-les-Pins, France. April 2-6 2002.